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Synthesis and Reactions of 1,2-Disubstituted Methylenecyclopropanes Prepared via Intramolecular Cyclopropanation of Allenic Diazoacetates.

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Abstract: Diazoacetates derived from α- or β- allenic alcohols, prepared using the glyoxylic acid chloride p-toluenesulfonylhydrazone method, undergo regioselective intramolecular cyclopropanation in the presence of a copper (II) catalyst in refluxing toluene, leading to synthetically useful di- or trisubstituted methylenecyclopropyl lactones. The diastereoselectivity of the process has been studied. © 1997 Elsevier Science Ltd.

Methylenecyclopropanes have been shown to possess extremely useful reactivity in organic synthesis, as illustrated by the numerous metal catalyzed processes affecting one of the three reactive sites (distal or vicinal cyclopropane bond and the olefin) of these highly strained carbocycles.[1]

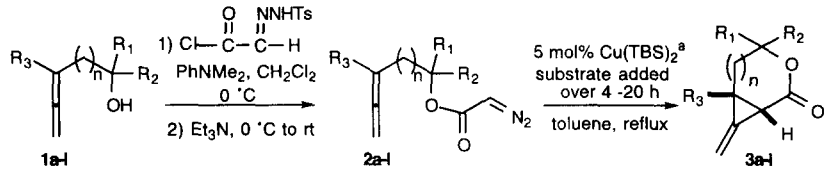
As a result, a number of strategies have been developed for the synthesis of methylenecyclopropanes. Among these general methods, routes involving a direct cyclopropanation of allenes are potentially the most efficient. Contributions in this field include some examples of Simmons-Smith cyclopropanations of allenes which often lead to the spirocyclic hydrocarbons, hydroxyl directed cyclopropanation of α-allenic alcohols,[2] addition of halogenocarbenes or carbenoids to allenes as well as the photochemical or Pd(II) catalyzed reaction with diazoesters.[2]

Whereas intramolecular cyclopropanation of allylic and homoallylic diazoacetates have been the subject of numerous investigations in recent years,[3] the corresponding reaction for allenes has not been studied to our knowledge. Following our studies on intramolecular [3+2] cycloadditions of allyl and propargyl ethers derived from diastereomeric methylenecyclopropyl carbinols[1d,e] and hydrostannation of methylenecyclopropanes,[1k] it became desirable to synthesize methylenecyclopropanes incorporating additional substitution and we report herein our preliminary results on the intramolecular cyclopropanation of diazoacetates derived from allenic alcohols.

Allenic alcohols **1a-i**, prepared by conventional methods,[4] were converted to their diazoesters in good yields using the procedure reported by Corey and Myers.[5] In the case of the tertiary alcohol **1b**, a two fold excess of the reagents was necessary to achieve efficient conversion.

We initially examined rhodium catalysts in the intramolecular cyclopropanation of diazoacetates **2**. Unfortunately use of $Rh_2(OAc)_4$ or $Rh_2(OOct)_4$ in refluxing dichloromethane, with slow addition of the substrate over 12 hours or more, gave complex reaction mixtures with only a trace of the desired methylenecyclopropanes **3**. Other rhodium catalysts were not tested in our preliminary studies since we found

that the intramolecular cyclopropanations can be performed using bis-(N-*tert*-butylsalicylaldiminato) copper (II) as a catalyst, as originally reported for allylic diazoacetates.[5] Thus, diazoesters **2a** and **2b** gave good to excellent yields of the corresponding substituted 5-methylene-3-oxabicyclo[3.1.0]hexan-2-one **3a** or 6-methylene-3-oxabicyclo[4.1.0]heptan-2-one structures **3b** exclusively, demonstrating that the cyclopropanation has occurred regioselectively at the more substituted double bond of the allenic moiety. However, diazoester **2c** gave a complex mixture of products rather than the corresponding 7-methylene-3-oxabicyclo[5.1.0]octan-2-one **3c**.



1a-l **2a-l** **3a-l**

Compound	n	R_1	R_2	R_3		yield[b]		yield[b]	d.r[c]
1a	0	-$(CH_2)_5$-		H	**2a**	66%[d]	**3a**	94%	
1b	1	Me	Me	H	**2b**	39%[e]	**3b**	76%	
1c	2	H	H	H	**2c**	61%	**3c**	--[f]	
1d	0	H	Ph	H	**2d**	63%	**3d**	84%	50/50
1e	0	H	cHex	H	**2e**	82%	**3e**	82%	55/45
1f	1	H	*t*-Bu	H	**2f**	82%	**3f**	83%	53/47
1g	0	H	Ph	H	**2g**	79%	**3g**	54%	75/25
1h	0	H	cHex	Me	**2h**	79%	**3h**	89%	65/35
1i	0	H	cHex	Me_3Si	**2i**	80%	**3i**	90%	80/20
1j	0	H	Ph	Me_3Si	**2j**	52%	**3j**	90%	**85/15**
1k	0	H	*t*-Bu	Me_3Si	**2k**	74%	**3k**	78%	**94/ 6**
1l	0	H	cHex	$tBuPh_2Si$	**2l**	64%	**3l**	60%	**90/10**

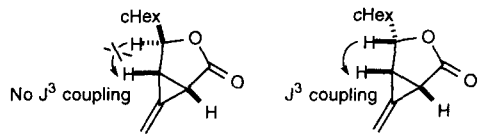
a) $Cu(TBS)_2$ = bis-(N-*tert*-butylsalicilylaldiminato) copper(II). b) Isolated yields of analytically pure products.
c) Diastereoisomeric ratio measured on the ^1H NMR spectra of the crude reaction mixture.
d) A two fold excess of the reagents was used. e) Yield based on ethyl pentadi-2,3-enoate (2 steps).
f) Complex reaction mixture.

Table 1

The intramolecular cyclopropanation of diazoacetates **2d**, **2e**, and **2f** proceeded in excellent yield, but the diastereoselectivity was poor. Improved diastereoselectivity was observed in the case of the secondary homoallenic diazoacetate **2g**. Substituents on the internal double bond of the allene also influenced the diastereoselectivity of the process. Thus, the methyl substituted allenic diazoacetate **2h** gave **3h** with a marginally better d.r compared to **3d** and with no diminution in yield. The trimethylsilyl substituted allenic diazoacetate **2i** gave **3i** as a 80/20 mixture of diastereomers in excellent yield, whereas the diastereomeric ratio increased to 90/10 in the case of **2l**, although the yield was reduced perhaps due to the steric bulk of the TBDPS group. Good diastereoselectivity was also observed for the conversion of **2j** to **3j**. The best d.r. was found for **3k**, which was obtained as a 94/6 mixture of diastereomers.

Fortunately the diastereomers of **3d**, **3e**, and **3f** were easily separated by flash chromatography and we

assigned their relative stereochemistry on the basis of the characteristic splitting patterns exhibited by the methine proton α to the ring oxygen of the methylenecyclopropyl lactones. No coupling is observed between the two hydrogens when they are trans whereas a J^3 coupling is seen when the hydrogens are cis (Scheme 1).

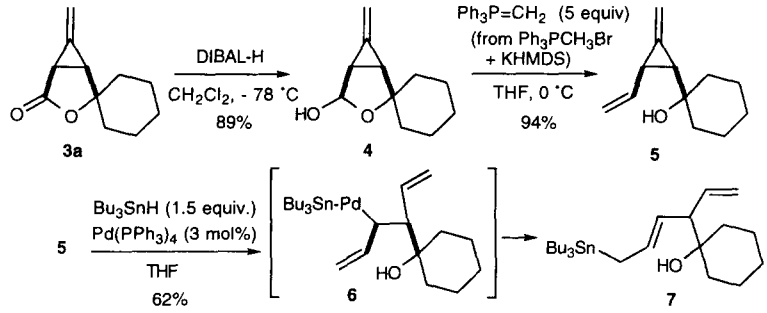


Scheme 1

For the trimethylsilyl substituted methylenecyclopropyl lactones **3i**, **3j**, and **3k**, assignment of the relative stereochemistry was less straightforward. For **3k** a strong NOE was observed between the TMS protons and the methine proton α to the ring oxygen, while only a very weak interaction between the TMS and the *t*-butyl protons was observed. This indicates that the TMS group and the *t*-butyl group have a trans relationship.

We have initiated preliminary investigations to exploit the use of the methylenecyclopropyl lactones generated by this reaction, in organic synthesis. Thus, reduction of the lactone **3a** to the lactol **4** with DIBAL-H was followed by exposure to an excess of methylenephosphorane (5 equiv.) (generated by treatment of the corresponding phosphonium salt with potassium hexamethyldisilazide (KHMDS)) in THF at 0 °C to afford the corresponding vinyl methylenecyclopropylcarbinol **5**.

We have recently reported that methylenecyclopropanes undergo a hydropalladation-rearrangement-reductive elimination in the presence of tin hydrides to furnish a novel route to homoallylstannanes.[1k] We have now examined the reaction **5** with Bu_3SnH in the presence of a catalytic amount of $Pd(PPh_3)_4$ and found that the allylstannane **7** is produced in 62% yield. It is particularly noteworthy that the use of a soluble palladium catalyst leads to reaction at only one of the two olefins present in **5**. Reaction at the more strained exocyclic olefin and regioselective rearrangement of the cyclopropylmethyl stannylpalladium intermediate generates an allylstannyl palladium complex **6** (as a σ or π-complex) which reductively eliminates regio- and stereoselectively to form the *trans* allylstannane **7** (Scheme 2).[6,7]



Scheme 2

In conclusion, we have shown in this preliminary study that diazoacetates derived from α- and β-allenic alcohols undergo regioselective cyclopropanation to give the corresponding methylenecyclopropyl lactones in good to excellent yields. The methylenecyclopropyl lactones can be converted to vinyl-methylenecyclopropylcarbinols whose hydrostannation affords an entry to novel allylstannanes. The importance of methylenecyclopropanes and allylmetal compounds in synthesis suggests that additional studies to improve

the diastereoselectivity of the process and to develop an enantioselective version of this reaction be carried out. These studies are now in progress and the results will be reported in due course.

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4. The allenic alcohols were prepared by conventional methods: For **1a,d,e** see ref. 2. β-allenic alcohols **1b** and **1f** were prepared from ethyl pentadi-3,4-enoate, respectively by addition of MeMgBr, or monoreduction with DIBAL-H followed by one-pot addition of PhMgBr: (a) Brandsma, L.; Verkruijsse, H.D. *Synthesis of Acetylenes, Allenes and Cumulenes*; Elsevier: Amsterdam, 1981. (b) Pyo, S.; Skowron III, J.F.; Cha, J.K. *Tetrahedron Lett.* **1992**, *33*, 4703. For the preparation of **1g,h,i** see: (c) Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Org. Chem.* **1982**, *47*, 2225. For the preparation of **1c** see: (d) Arseniyadis, S.; Goré, J.; Roumestant, M.L. *Tetrahedron* **1979**, *35*, 353.
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6. This compound is contaminated by a minor by-product which might be its (Z) isomer.
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